



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

94340d

Dallas District
4040 North Central Expressway
Dallas, Texas 75204-3145

October 7, 2003

Ref: 2004-DAL-WL-03

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. John R. Rains, R. Ph., CEO
Plum Creek Pharmaceuticals, Inc.
5211-B W. 9th
Amarillo, Texas 79106

Dear Mr. Rains:

On February 24 - 28, 2003, investigators of the U.S. Food and Drug Administration (FDA) and the Texas State Board of Pharmacy conducted an inspection of your firm. This inspection disclosed that your firm compounds various human and veterinary prescription drugs in various dosage forms and various strengths.

HUMAN DRUGS:

Although in the FDA Modernization Act of 1997, Congress had provided certain conditions under which compounded human drugs could be exempt from particular requirements of the Federal Food, Drug, and Cosmetic Act (the Act), (505, 502(f)(1), and 501(a)(2)(B)), as a result of a Supreme Court ruling last year, those exemptions are no longer available for compounded drugs. (See *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002)).

With the invalidation of section 503A and the exemptions it provided, FDA determined that it needed to issue guidance to the field and compounding industry on what factors the agency will consider in exercising its enforcement discretion regarding pharmacy compounding. This guidance in the form of Compliance Policy Guide (CPG), section 460.200, issued on June 7, 2002. As stated in this CPG, the nine factors listed are not intended to be exhaustive, and other factors may also be appropriate for consideration. Further, in some cases, even when a pharmacy's drug production practices are more analogous to pharmacy compounding, FDA may take action when FDA becomes aware of pharmacy compounding that could have an adverse effect on the public health.

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During the inspection, it was disclosed that your firm compounds Fentanyl with Naloxone "lollipops" in the following strengths:

- Fentanyl citrate 200 mcg; Naloxone hydrochloride 0.25 mg
- Fentanyl citrate 400 mcg; Naloxone hydrochloride 0.25 mg
- Fentanyl citrate 600 mcg; Naloxone hydrochloride 0.25 mg
- Fentanyl citrate 800 mcg; Naloxone hydrochloride 0.25 mg
- Fentanyl citrate 1200 mcg; Naloxone hydrochloride 0.25 mg
- Fentanyl citrate 1600 mcg; Naloxone hydrochloride 0.25 mg.

It was also disclosed that your firm compounds Fentanyl with Naloxone and Midazolam "lollipops" in the following strengths:

- Fentanyl citrate 200 mcg; Naloxone hydrochloride 0.25 mg; Midazolam 2.5 mg
- Fentanyl citrate 400 mcg; Naloxone hydrochloride 0.25 mg; Midazolam 5 mg

The agency is seriously concerned about the public health risks associated with the compounding of "lollipops" that contain Fentanyl and Naloxone and "lollipops" that contain Fentanyl, Naloxone, and Midazolam when such products are prepared for dispensing to the patient without the labeling and other packaging and patient safety features required by FDA for the FDA approved product (Fentanyl "lollipops").

The inspection disclosed that your firm prepares each type of "lollipop" referenced above in a heat sealed zip lock bag. The lollipops are packaged, ten at a time, in a larger heat sealed zip lock bag. None of these bags are child-proof. Even though the larger outer bag is labeled with your firm's name, the names and strengths of the active ingredients, a statement "Keep Out of the Reach of Children", and a lot code with expiration date, the products are not accompanied by such warnings and materials to assure restricted access to the product. The commercially available Fentanyl "lollipop" product is marketed with a child-resistant lock used to secure a storage space for the product in the patient's home. In addition, the commercially available product is marketed with a portable locking pouch for storage of a small amount of the product for immediate use and a child-resistant temporary storage bottle that permits the patient to safely store it until it can be properly disposed of. Detailed patient labeling supplied with the commercially available Fentanyl "lollipop" product not only describes how to use these materials, it discusses how to store it in the home, the proper way to use it, how to dispose of any remaining product after use, and what to do if a child or an adult accidentally takes it.

Our inspection disclosed that none of the safety measures mentioned above are provided by Plum Creek Pharmaceuticals, Inc. with their compounded Fentanyl "lollipop" products. In addition, although each "lollipop" has a sticker label around the lower region of the stick

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with the same information as described for the outer bag, this sticker could be peeled off or fall off, if wet. The commercially available Fentanyl "lollipop" has the product name engraved in the stick. In the case of an accidental exposure or overdose with your compounded product, there could be no means for identifying the product.

The commercially available Fentanyl "lollipop" product is intended for use in opioid-tolerant patients with breakthrough cancer pain. This population represents the population for whom safe use has been documented. The effects of incorporating Naloxone into the formulation have not been studied for safety and may promote the use in opioid-naïve patients if perceived as safe due to the presence of Naloxone.

There have been reports of serious adverse effects, including death, due to accidental pediatric exposure to the commercially available Fentanyl "lollipop" product in doses comparable to the doses being made available in your compounded products. The child-resistant lock, detailed patient labeling, and other materials required by the FDA for the commercially available Fentanyl "lollipop" were intended to minimize the risk to children.

One of your "lollipop" products is being compounded with Midazolam, a benzodiazepine. The combination of an opioid and benzodiazepine is known to increase the central nervous system depressant effects that occur with both drug groups. This greatly increases the risk of serious and life-threatening adverse events including hypoventilation, hypotension, and death. This enhanced risk is present for patients using the product as well as for children accidentally exposed. There is also a report (Gilliland et al., *Anaesthesia* 52(4):389, 1997) that Midazolam may potentiate opioids further increasing risk.

In light of the above, your compounded Fentanyl with Naloxone and Fentanyl with Naloxone and Midazolam "lollipops", in dosage strengths described above, are misbranded within the meaning of section 502(a) of the Act since its labeling is false and misleading in that it fails to reveal facts material with respect to consequences that may result from the use of the article under conditions of use prescribed in the labeling or under such conditions of use as are customary or usual. They are also misbranded within the meaning of section 502(f)(2) in that the labeling does not provide adequate warnings against use by children where its use may be dangerous to health in that it lacks information on the proper storage and disposal of the drug to avoid accidental ingestion by children. These products are further misbranded within the meaning of section 502(j) in that they are dangerous to health when used in the manner prescribed in their labeling.

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ANIMAL DRUGS:

Your firm also compounds veterinary prescription drug products, compounded with the use of bulk active pharmaceutical ingredients (APIs). The current inspection documented the compounding of the following drugs:

- Methyltestosterone 50mg tablets – this drug was compounded and shipped to a veterinary clinic. A total of 9,856 tablets were compounded in 2 batches, one in November 2002, and a second in January 2003, and;
- Yohimbine hydrochloride 10mg/ml injection – this drug was compounded and shipped to veterinary clinics in 13 states in the 90 days prior to the inspection date. A total of 8 production batches accounted for production of 32,220 ml of product.

The veterinary drugs compounded and distributed by your firm are new animal drugs within the meaning of Section 201(v) of the Act. These drugs are adulterated under Section 501(a)(5) of the Act because they are unsafe within the meaning of Section 512 of the Act.

Under Section 512, a new animal drug is deemed to be unsafe unless an approved New Animal Drug Application (NADA) is in effect for the specific product in question. None of the animal drugs compounded and distributed by your firm are the subject of an approved NADA.

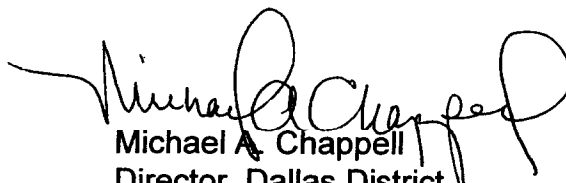
The only legal compounding of animal drugs is provided under the Animal Medicinal Drug Use Clarification Act and its implementing regulations at 21 CFR Part 530, Extralabel Drug Use in Animals. Our investigation found that you did not comply with these requirements. For example, 21 CFR 530.13(a) requires that the compounding be conducted using approved animal or human drug products. However, your firm compounded with the use of bulk APIs, which is not permitted. In addition, the compounded drug products were not labeled with directions for use specified by the veterinarian, including the animal or animals in which the drug is intended to be used, as required by 21 CFR 530.12(c).

The above violations are not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure that all your drug products are in compliance with federal laws and regulations. Failure to promptly correct all violations and prevent future violations may result in regulatory action without further notice, such as seizure and/or injunction.

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Please notify this office within 15 working days of receipt of this letter of the specific steps you will take to correct these violations, including an explanation of each step being taken to prevent the recurrence of the violations. You should address your reply to this letter to the U. S. Food and Drug Administration, Attention: Jim Lahar, Compliance Officer, at the above letterhead address.

Sincerely,



Michael A. Chappell
Director, Dallas District

MAC:JRL